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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,843	05/04/2005	Frederick S. Hagen	017881-001110US	7354

20350 7590 01/06/2009

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
01/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,843	HAGEN, FREDERICK S.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,39-44 and 46-54* is/are pending in the application.

4a) Of the above claim(s) *11, 14-35 and 47-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,13,36,37,39-44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-37,39-44 and 46-54* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 9/29/08 has been entered in full. Claims 1, 34, and 36 are amended. Claims 38 and 45 are canceled.

Claims 1-37, 39-44 and 46-54 are pending in the instant application.

Claims 11, 14-35 and 47-54 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim (see pg 2 of the 3/28/08 Office Action).

Claims 1-10, 12, 13, 36, 37, 39-44 and 46 are under consideration, in so far as they are drawn to the elected species.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (3/28/08).

All rejections of claims 38 and 45 are moot in view of Applicant's cancellation of these claims.

The objection to claim 1 at pg 1 is *withdrawn* in view of Applicant's amendments to the claim.

The rejection of claims 1-10, 12, 13, 36, 37, 39-44 and 46 under 35 U.S.C. § 112, first paragraph at pg 3-5 for failing to provide enablement for the full scope of the claims is *withdrawn* in view of Applicant's amendments to independent claim 1.

The rejection of claims 1-7, 12, 13, 36, 37, 39-44 and 46 under 35 U.S.C. § 102(b) at pg 5-9 as anticipated by Hooper et al (1997) is *withdrawn* in view of Applicant's amendments to independent claim 1; Applicant's persuasive arguments at page 16 of the response that the specification defines an "allosteric effector of the membrane" as an agent that binds to a membrane protein; and further that Hooper et al (1997) does not teach screening for agents that bind to a membrane protein.

The rejection of claims 8-10 under 35 U.S.C. § 103(a) at pg 9-10 as being unpatentable over Hooper et al (1997) in view of Mucke et al (U.S. Patent 6,175,057) is *withdrawn* in view of Applicant's amendments to independent claim 1; Applicant's

persuasive arguments at page 16 of the response that the specification defines an "allosteric effector of the membrane" as an agent that binds to a membrane protein; and that Hooper et al (1997) does not teach screening for agents that bind to a membrane protein.

New rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12, 13 and 36-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al, 1997. Biochem J. 321: 265-279 (cited on the 9/26/07 IDS) and further in view of Hsieh et al (U.S. Patent No. 6,576,430; published June 10th, 2003 and filed on November 20th, 2000) and further in view of Zhang et al (April 2001. Chemistry & Biology. 8: 391-397).

The instant claims have been amended such that independent claim 1 (and thus, each dependent claim) includes the limitation that the method includes "identifying the agent that is an allosteric effector of the membrane protein". The specification teaches that the term ""[a]llosteric effector of the membrane protein" thus refers to an agent that specifically binds to the membrane protein, or a functional fragment thereof, and changes its conformation such that processing by one or more processing enzyme of the membrane protein is altered" (pg 13, lines 26-31). The specification teaches that "[i]dentification of allosteric effectors can be performed as a secondary screen on agents that have been identified as effectors of membrane protein processing. Alternatively, compound libraries or peptide expression libraries can be prescreened to identify agents that bind to a potential allosteric site on the membrane protein" (pg 36, lines 20-24). Thus, the new limitation in claim 1 can be performed prior to or after the other method steps in the claiming. Applicant's response also acknowledges this;

specifically, page 15 states "there is no required order for carrying out the presently claimed method steps".

Hooper et al review "[m]embrane protein secretases" (see Title), including both ACE (angiotensin-converting enzyme), which is the elected species of membrane protein under consideration, and APP (amyloid precursor protein). Hooper et al further teach in a section titled "Secretase Assays" that "[t]he majority of studies on membrane protein secretases have employed whole-cell systems utilizing either natural or recombinant cell lines that express both the membrane protein and its secretase. The activity of the secretase is usually detected and quantified by monitoring the presence of the cleaved, hydrophilic form of the membrane protein in the cell medium ... the effect of various agents (e.g. phorbol esters, transport inhibitors, etc) on the activity of the secretase can be studied" (pg 275). Hooper et al further teach, "...release of TGF-α, L-selectin, IL6R and APP from the surface of CHO cells can be blocked by both metallo-protease inhibitors (TAPI-2 and 1,10-phenanthroline) and serine-protease inhibitors..." On page 271, Table 2, Hooper et al list metalloproteinase inhibitors and the membrane proteins they act on; for example, TAPI-2 acts on release of TGF-α, APP, L-selectin, IL6R and ACE. Thus, Hooper et al teach methods for identifying an agent that alter membrane protein processing that comprises contacting a "various agents" with CHO animal cells that express a membrane protein (e.g., ACE or APP) and its respective secretase and detecting altered (e.g., blocked) processing when the cell is contacted with said agent.

Hooper et al do not teach identifying an agent that is an allosteric effector of the membrane protein as defined by the instant specification; i.e., that the agent binds to the membrane protein (e.g. ACE or APP) and changes its conformation such that processing is altered.

Hsieh et al teach, "...changes in refractive index can be used to detect binding of ligand to immobilized receptors when the receptor (e.g. a binding protein) or the receptor-surface complex undergoes a conformational change upon binding to the ligand. The conformational change is detectable even when the ligand is small and the receptor is large" (col 2, lines 57-63). Hsieh et al teach, "The term "receptor" as used i

the art typically refers to the larger of the two binding partners, and it is generally the member of the binding pair which undergoes conformational change upon binding" (col 3, lines 46-49). Hsieh et al teach, "[l]igands for use in the invention are preferably but not necessarily less than about 1500 molecular weight, more preferably about 30-400 molecular weight, and include amino acids and peptides, nucleotides and oligonucleotides, sugars, ions and other small moieties known in the art" (col 4, lines 58-63).

Zhang et al teach "...the vast majority of enzymes that mediate post-translational modification of other proteins operate on multiple substrates. This fact places a fundamental limitation on the biological specificity that one can achieve using an enzyme-targeted inhibitor. An alternative strategy would be to manipulate the post-translational modification of proteins with compounds that recognize the substrate rather than the enzyme" (pg 391).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method combining the method taught by Hooper et al comprising contacting a "various agents" with CHO animal cells that express a membrane protein (e.g., ACE or APP) and its respective secretase and detecting altered (e.g., blocked) processing when the cell is contacted with said agent), and the method of screening taught by Hsieh et al, in order to determine if an agent that modulates membrane protein processing is also an allosteric modulator of the membrane protein (e.g. ACE or APP). The person of ordinary skill in the art would have been motivated to make such a modification in order to identify an agent that alters membrane protein (e.g., ACE or APP) processing that is more specific for the membrane protein (as taught by Zhang), as opposed to the less specific protease inhibitors taught by Hooper et al. The person of ordinary skill in the art would have a reasonable expectation of success because the skilled artisan would merely need to perform the two separate methods in succession (in either order) with the same membrane protein (e.g., ACE or APP) and agents.

Claims 2 and 3 each encompasses a method of claim 1 wherein the detecting of the altered processing comprises assessing the relative presence of a membrane

protein fragment released from the surface of the cell. In the teachings of Hooper described above, the blockage of release of the ectodomain of the membrane proteins indicates that the relative presence of the membrane protein fragment has been detected; therefore, claims 2 and 3 are included in the rejection for the same reason as claim 1 above.

Claim 4 depends from claim 1 and encompasses "a membrane protein processing enzyme" that is "a protease". The teachings of Hooper described are directed to enzymes that are proteases; therefore, claim 4 is included in the rejection for the same reason as claim 1 above.

Claim 5 depends from claim 1 and recites "wherein the altered membrane protein processing results in a decreased production of a fragment of the membrane protein released from the cell surface". In the teachings of Hooper described above, the blockage of release of the ectodomain of the membrane proteins inherently results in decreased production of the released fragment; therefore, claim 5 is included in the rejection for the same reason as claim 1 above.

Claims 6 and 7 depend from claim 5 and limit the released fragment to one that is "associated with an increased risk of disease" (claim 6) and further wherein the disease is diabetes (claim 7). Hooper et al further teaches, that "[i]n certain diseases such as ... diabetes mellitus ... the levels of soluble ACE in plasma are known to be altered" (pg 271). ACE was used as an exemplary membrane protein with respect to claim 1 above; therefore, claims 6 and 7 are included in the rejection for the same reason as claim 1 above.

Claim 12 depends from claim 1 and limits the agent to a "small molecule". As described above, Hsieh et al suggest the use of ligands that are small moieties, which is encompassed by the term "small molecule"; therefore, claim 12 is included in the rejection for the same reason as claim 1 above.

Claim 13 depends from claim 1 and limits the agent to a "biomolecules". The specification teaches that biomolecules includes molecules that exist or can be produced by living systems "as well as structures derived from such molecules" ([¶ 46 of the published application]). As described above, Hsieh et al suggest use of amino acid

and peptides, which are biomolecules as defined by the instant specification; therefore, claim 12 is included in the rejection for the same reason as claim 1 above.

Claims 36 and 37 each depend from claim 1 and limit the host cell to either a mammalian (claim 36) or a recombinant (claim 37). As described above, Hooper teaches use of assays using "recombinant cell lines" (which are recombinant and isolated) and "CHO cells" which are mammalian. Therefore, claims 36 and 37 are included in the rejection for the same reason as claim 1 above.

Claim 39 depends from claim 1 and limits the method to one "wherein the agent is contacted with the host cell under substantially physiological conditions". The specification teaches (¶ 65) that such conditions refer to those "normally present, or that substantially approximate those normally present, in an extracellular space, on an extracellular surface (e.g., on a cell membrane), in a Golgi network, secretory vesicle, and/or in a complex biological fluid". As such, the phrase "substantially physiological condition" broadly encompasses any screening that takes place with a cell-bound membrane protein, because such is "on an extracellular surface". Therefore, claim 39 is included in the rejection for the same reason as claim 1 above.

Claim 46 depends from claim 1 and limits the method to one wherein detection of altered processing comprises use of a "flow sorter". Hooper further teaches that "disappearance of the membrane-bound form can be followed by, for example, flow cytometry" (pg 275). With respect to claim 46, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method combining the method taught by Hooper et al comprising contacting a "various agents" with CHO animal cells that express a membrane protein (e.g., ACE or APP) and its respective secretase and detecting altered (e.g., blocked) processing when the cell is contacted with said agent), and further wherein the disappearance of the membrane-bound form is followed by flow cytometry, and the method of screening taught by Hsieh et al, in order to determine if an agent that modulates membrane protein processing is also an allosteric modulator of the membrane protein (e.g. ACE or APP). The person of ordinary skill in the art would have been motivated to make such a modification in order to identify an agent that alters membrane protein (e.g., ACE or APP) processing that is

highly specific for the membrane protein (as taught by Zhang et al), as opposed to the general protease inhibitors taught by Hooper et al. The person of ordinary skill in the art would have a reasonable expectation of success because the skilled artisan would merely need to perform the two separate methods in succession with the same membrane protein (e.g., ACE or APP) and agents.

Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al, 1997. Biochem J. 321: 265-279 (cited on the 9/26/07 IDS) and further in view of Hsieh et al (U.S. Patent No. 6,576,430; published June 10th, 2003 and filed on November 20th, 2000) and further in view of Zhang et al (April 2001. Chemistry & Biology. 8: 391-397), as applied to claim 1 above, and further in view of Mucke et al, U.S. Patent 6,175,057 (published January 16, 2001; cited on the 9/20/07 IDS).

The teachings of Hooper are described above. Hooper further teaches that "considerable effort is being expended to find inhibitors of APP β-secretase and γ-secretase with a view to reducing amyloid burden for Alzheimer's disease" (pg 277). Hooper does not teach a method of screening wherein an agent that alters processing is from a compound library.

Mucke et al teach methods of screening for agents that affect molecular phenomenon associated with Alzheimer's disease. Mucke et al teach that candidate agents include those from "libraries of synthetic or natural compounds" (col 16, lines 44-45) or "combinatorial libraries" including those made by "chemical means" (col 16, lines 53-54). Mucke et al further teach that candidate agents include those with "functional groups necessary for structural interaction with proteins" (col 16, line 33). The term "natural products" as recited in claim 10 encompasses "natural compounds" as taught by Mucke et al.

For the reasons described above for claim 1, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method combining the method taught by Hooper et al comprising contacting a "various agents" with CHO animal cells that express a membrane protein (e.g., APP) and its respective secretase and detecting altered (e.g., blocked) processing when the cell is

contacted with said agent), and the method of screening taught by Hsieh et al, in order to determine if an agent that modulates membrane protein processing is also an allosteric modulator of the membrane protein (e.g. APP). It would have further been obvious to the person of ordinary skill in the art at the time the invention was made to substitute any of the agents suggested by Mucke et al (including combinatorial chemical or natural compound libraries) for the "various agents" used in the method taught by Hooper et al and the "ligands" taught by Hsieh et al. The person of ordinary skill in the art would be motivated to do so in order to identify new inhibitors of the secretases involved in Alzheimer's disease. Further, a person of ordinary skill in the art would have a reasonable expectation of success because the method simply requires using the libraries described by Mucke et al in the screening assays fully described by Hooper et al and Hsieh et al.

Claims 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al, 1997. Biochem J. 321: 265-279 (cited on the 9/26/07 IDS) and further in view of Hsieh et al (U.S. Patent No. 6,576,430; published June 10th, 2003 and filed on November 20th, 2000) and further in view of Zhang et al (April 2001. Chemistry & Biology. 8: 391-397) as applied to claim 39 above, and further in view of Arribas et al (1996; Journal of Biological Chemistry. 271(9): 11376-11382; cited previously).

Claims 40 and 41 depend from claim 39 and each encompass conditions comprising the presence of "serum".

The teachings of Hooper et al, Hsieh et al and Zhang et al are described above. While Hooper et al teaches assays using CHO cells, and that the presence of the cleaved membrane protein is detected in the cell medium, Hooper et al does not specify the nature of said cell medium.

Arribas et al teach that "CHO cells were cultured in monolayers in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum" (pg 11377).

For the reasons described above for claim 39, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method combining the method taught by Hooper et al comprising contacting a "various

agents" with CHO animal cells that express a membrane protein (e.g., ACE) and its secretase and detecting altered (e.g., blocked) processing when the cell is contacted with said agent), and the method of screening taught by Hsieh et al, in order to determine if an agent that modulates membrane protein processing is also an allosteric modulator of the membrane protein (e.g. ACE or APP). It would have further been obvious to use CHO animal cells cultured in cell medium comprising serum as taught by Arribas et al. The person of ordinary skill in the art would have been motivated to make such a modification because Hooper et al suggest use of CHO cells and monitoring the cleavage in the cell medium, but fail to specify the cell medium for CHO cells, and Arribas et al teaches cell medium for culturing CHO cells that includes serum. The person of ordinary skill in the art would have had a reasonable expectation of success because the skilled artisan would merely need use the medium as specified by Arribas et al in the method taught by Hooper et al.

Claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al, 1997. Biochem J. 321: 265-279 (cited on the 9/26/07 IDS) and further in view of Hsieh et al (U.S. Patent No. 6,576,430; published June 10th, 2003 and filed on November 20th, 2000) and further in view of Zhang et al (April 2001. Chemistry & Biology. 8: 391-397) as applied to claim 2 above, and further in view Gosling et al (1990. Clin Chem. 36(8): 1408-1427).

Claims 42-44 depend from claim 2 and each encompass the embodiment recited in claim 44, wherein the membrane protein fragment presence is assessed using at least two labeled antibodies for two different epitopes of the membrane protein or a membrane protein fragment.

The teachings of Hooper et al, Hsieh et al and Zhang et al are described above.

As described above for claim 2, the teachings of Hooper et al comprise assessing the relative presence of a membrane protein fragment released from the surface of the cell. Hooper et al further teach distinguishing between the "hydrophilic and amphipathic forms of a protein on SDS/PAGE is to perform immunoelectrophoretic blot analysis with site-specific antibodies which selectively recognize regions of the

protein either side of the secretase cleavage site … an antibody to the cytosolic form will cross-react only with the full-length amphipathic form" (pg 278). The term "ratio" broadly encompasses any comparison of relative quantities. Analyzing the binding of antibodies to either side of the secretase cleavage site would determine a ratio of the relative quantities of the detection signal of the antibodies.

Hooper et al does not teach that the antibodies are "labeled".

Gosling et al teach a wide-variety of labeled antibodies (see entire document, specifically "Group 2" on page 1410).

For the reasons described above for claim 2, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method combining the method taught by Hooper et al comprising contacting a "various agents" with CHO animal cells that express a membrane protein (e.g., ACE) and its secretase and detecting altered (e.g., blocked) processing when the cell is contacted with said agent), and the method of screening taught by Hsieh et al, in order to determine if an agent that modulates membrane protein processing is also an allosteric modulator of the membrane protein (e.g. ACE or APP). It would have further been obvious to assess the membrane protein processing using site-specific antibodies that which selectively recognize regions of the protein either side of the secretase cleavage site (as taught by Hooper et al) and to further use labeled antibodies as taught by Gosling et al. The person of ordinary skill in the art would have been motivated to make such further modifications because Hooper et al suggests use of the site-specific antibodies as one of several alternatives for assessing membrane protein processing but is silent as to how to detect the antibodies, and Gosling teaches labels for detecting antibodies. The person of ordinary skill in the art would have had a reasonable expectation of success because one would merely need to use one alternative suggested by Hooper et al, and supply a detection reagent (labeled antibodies) not specified by Hooper et al but long known in the art as taught by Gosling et al.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646